



Analysis of vitamin D-binding protein (*VDBP*) gene polymorphisms in Korean women with and without endometriosis

Min-Chul Cho^{1,2}, Jin Hyun Kim^{2,3}, Myeong Hee Jung³, In Ae Cho⁴, Hyen Chul Jo⁵, Jeong Kyu Shin^{2,6}, Soon Ae Lee^{2,6}, Won Jun Choi^{2,6}, Jong Hak Lee^{2,6}

¹Department of Laboratory Medicine, Gyeongsang National University Hospital and Gyeongsang National University College of Medicine, Jinju; ²Institute of Health Sciences, Gyeongsang National University, Jinju; ³Biomedical Research Institute and ⁴Department of Obstetrics and Gynecology, Gyeongsang National University Hospital, Jinju; ⁵Department of Obstetrics and Gynecology, Gyeongsang National University Changwon Hospital, Changwon; ⁶Department of Obstetrics and Gynecology, Gyeongsang National University Hospital and Gyeongsang National University College of Medicine, Jinju, Korea

Objective: Vitamin D-binding protein (*VDBP*) mediates various biological processes in humans. The goal of this study was to investigate whether *VDBP* gene polymorphisms could predispose Korean women to endometriosis.

Methods: We prospectively enrolled women with endometriosis (n = 16) and healthy controls (n = 16). Total serum 25-hydroxyl vitamin D (25(OH)D) concentrations were measured using an Elecsys vitamin D total kit. Levels of bioavailable and free 25(OH)D were calculated. Concentrations of *VDBP* were measured using a vitamin D BP Quantikine ELISA kit. DNA was extracted using a DNeasy blood & tissue kit. Two single-nucleotide polymorphisms (SNPs; rs4588 and rs7041) in *GC*, the gene that codes for *VDBP*, were analyzed using a TaqMan SNP genotyping assay kit. The functional variant of *VDBP* was determined based on the results of the two SNPs.

Results: Gravidity and parity were significantly lower in the endometriosis patients than in the control group, but serum CA-125 levels and the erythrocyte sedimentation rate were significantly higher. Total serum 25(OH)D levels in the endometriosis patients were significantly lower than in the control group. However, serum bioavailable 25(OH)D, free 25(OH)D, and *VDBP* levels did not differ significantly between the endometriosis and control groups. The genotypes and allele frequencies of *GC* were similar in both groups.

Conclusion: Korean women with endometriosis had lower total serum 25(OH)D concentrations than controls. Neither serum *VDBP* concentrations nor polymorphisms in the gene coding for *VDBP* were associated with endometriosis. Further studies are needed to investigate the pathophysiology and clinical implications of 25(OH)D and *VDBP* in endometriosis.

Keywords: Endometriosis; Genetic polymorphism; Vitamin D; Vitamin D-binding protein

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Corresponding author: **Won Jun Choi**

Department of Obstetrics and Gynecology, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, 79 Gangnam-ro, Jinju 52727, Korea
Tel: +82-55-750-8147 Fax: +82-55-759-1118 E-mail: choiwj@gnu.ac.kr

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Introduction

Endometriosis is a chronic, benign, estrogen-dependent, inflammatory disease affecting approximately 10% of reproductive-age women and 35%–50% of women with pelvic pain and infertility. Endometriosis, which is defined as growth of endometrial tissue outside the uterine cavity, often results in a vast array of gynecological problems, including dyspareunia, dysmenorrhea, pelvic pain, and infertility [1].

The cause of endometriosis is not completely clear. Numerous hypotheses have been proposed to explain the presence of ectopic endometrial tissue and stroma. For example, it has been hypothesized

that retrograde menstruation and metaplasia play a role in the formation of ectopic endometrium in endometriosis [2]. However, retrograde menstruation alone is unable to explain all instances of endometriosis. Additional factors such as genetic and immune differences need to be invoked to account for the fact that many women with retrograde menstruation do not have endometriosis [3].

The observation that autoimmune diseases are more common in women with endometriosis supports the possibility that the pathogenesis of endometriosis may involve a defective immune response [4]. Regurgitation of endometrial cells into the peritoneum can trigger an inflammatory response that recruits activated macrophages and leukocytes locally [5,6]. This inflammatory response may cause defective “immune-surveillance,” which prevents elimination of menstrual debris and promotes the implantation and growth of endometrial cells at ectopic sites [7].

Humans acquire vitamin D from exposure to sunlight and dietary intake. Acquired vitamin D is metabolized in the liver, resulting in 25-hydroxyl vitamin D (25(OH)D) [8,9]. Most (85%–90%) of circulating 25(OH)D is tightly bound to vitamin D-binding protein (VDBP), with a smaller amount (10%–15%) loosely bound to albumin. Less than 1% of circulating vitamin D exists in a free unbound form [10]. The fraction not bound to VDBP (free and albumin-bound forms) is considered as bioavailable 25(OH)D.

Vitamin D is a multipotent vitamin that has a hormone-like function, including endocrine functions, regulation of cell replication, and immune modulation. The effects of vitamin D on the immune system and immune-related diseases have become the subject of a large number of studies. In this context, it has been discovered that supplementation with 1,25(OH)₂D₃ could prevent both the initiation and progression of experimental autoimmune encephalomyelitis and collagen-induced arthritis in experimental models of multiple sclerosis and rheumatic arthritis, respectively [11,12].

In humans, VDBP, originally known as GC-globulin (group-specific component), is encoded by the *GC* gene [13]. VDBP belongs to the albumin gene family, together with human serum albumin and alpha-fetoprotein. It is a multifunctional protein found in plasma, ascitic fluid, and cerebrospinal fluid, as well as on the surface of numerous cell types. VDBP is able to bind various forms of vitamin D, including ergocalciferol (vitamin D₂), cholecalciferol (vitamin D₃), 25-hydroxylated forms (calcifediol), and 1,25(OH)₂D₃ (calcitriol, the active form). The majority of vitamin D in the blood is bound to VDBP, which transports vitamin D metabolites from the skin, liver, and kidney to various target tissues [14]. VDBP is also known to mediate various biological functions in humans, including immune modulation, osteoclast activation, activation of chemotaxis, and fatty acid transport [15].

VDBP is the precursor molecule of a potent macrophage-activating factor [16] that is highly tumoricidal against various malignancies

through its ability to inhibit endothelial angiogenesis [17] and stimulate inflammation-primed phagocytic activity of tumoricidal macrophages [18]. Therefore, researchers in a previous study hypothesized that VDBP might play an important role in colorectal cancer initiation and progression, either alone or in combination with vitamin D [19].

The *GC* gene, which encodes VDBP, is highly polymorphic. Polymorphic VDBP proteins differ in their affinity for the 1,25(OH)₂D metabolite. Two common coding single-nucleotide polymorphisms (SNPs)—rs7041 (Asp416Glu) and rs4588 (Thr420Lys)—are correlated with circulating vitamin D levels. In addition, the combination of the two SNPs, rs7041 and rs4588, produces three variant combinations (Gc1s, Gc1f, and Gc2). These variants provide different binding affinities for vitamin D metabolites. It has been reported that Gc1f has the greatest affinity, followed by Gc1s and Gc2 [20]. A previous study has demonstrated that *GC* SNPs may affect blood plasma vitamin D levels [21], implying that they could be a risk factor related to the pathogenesis of endometriosis [22].

Endometriosis is a multifactorial disease in which local inflammatory processes appear to play a key role in development and progression [6]. Increasing interest in vitamin D has emerged because of its role as an immune modulator [23]. Although few studies have investigated the correlations of *VDBP* gene polymorphisms with bioavailable 25(OH)D and free 25(OH)D in patients with endometriosis, Faserl et al. [24] suggested that *VDBP* gene polymorphisms might be a risk factor for endometriosis.

Based on this observation, we hypothesized that *VDBP* gene polymorphisms might have relationships with endometriosis, as well as serum vitamin D (total 25(OH)D, bioavailable 25(OH)D, and free 25(OH)D) concentrations. To test this hypothesis, we analyzed serum vitamin D levels and *VDBP* gene polymorphisms in 16 patients with endometriosis and 16 healthy controls.

Methods

1. Study subjects

This was a prospective study conducted at the Gyeongsang National University Hospital, Jinju, Korea. Whole blood and serum samples were collected from 16 patients with endometriosis and 16 healthy controls between February 2017 and March 2019. All patients with endometriosis had a definitive diagnosis made based on a pathological review of their surgical specimens. Healthy controls were defined as women who visited Gyeongsang National University Hospital for a health checkup without having any symptoms of endometriosis. Healthy controls were enrolled in this study only if they did not have any disease (such as uterine leiomyomas; hypertension; diabetes; multiple sclerosis; autoimmune disorders; or coronary, hepatic, or renal disease as assessed through a questionnaire and laboratory tests) that could affect serum

VDBP concentrations. If other underlying diseases were present, patients were excluded from this study. In addition, all potential participants were surveyed to determine whether they had a recent history of taking vitamin D supplements and hormonal pills. Only those who did not have such a history were included in this study. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital (IRB No. GNUH 2017-01-004).

2. Serum total 25(OH)D assay and calculation of bioavailable and free 25(OH)D

Each serum sample was aliquoted into two tubes and stored at -80°C until it was analyzed for VDBP and total 25(OH)D. Concentrations of VDBP were measured using a human vitamin D BP Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol. Measurements of total serum 25(OH)D concentrations were performed using an Elecsys vitamin D total kit with a Cobas e602 module (Roche Diagnostics, Mannheim, Germany). This was an electrochemiluminescent assay with ruthenium-labeled VDBP, biotin-labeled vitamin D, and streptavidin-coated microparticles.

Levels of bioavailable and free 25(OH)D were calculated from the total measured 25(OH)D, VDBP, and serum albumin concentrations using the following equations [25,26].

$$\text{Bioavailable 25(OH)D} = \text{albumin-bound 25(OH)D} + \text{free 25(OH)D} \\ = (\text{albumin} \times K_{\text{albumin}} + 1) \times \text{free 25(OH)D}$$

$$\text{Free 25(OH)D} = \frac{-b + \sqrt{b^2 - 4ac}}{2a}$$

$$a = K_{\text{VDBP}} \times K_{\text{albumin}} \times \text{albumin} + K_{\text{VDBP}}$$

$$b = K_{\text{VDBP}} \times \text{VDBP} - K_{\text{VDBP}} \times \text{total 25(OH)D} + K_{\text{albumin}} \times \text{albumin} + 1$$

$$c = -\text{total 25(OH)D}$$

$$K_{\text{VDBP}} \text{ [for genotype-constant bioavailable 25(OH)D]} = 0.7 \times 10^9 \text{ M}^{-1}$$

To calculate the genotype-specific bioavailable 25(OH)D levels, GC

genotype-specific VDBP binding affinity (K_{VDBP1f} , $1.12 \times 10^9 \text{ M}^{-1}$; K_{VDBP1s} , $0.6 \times 10^9 \text{ M}^{-1}$; K_{VDBP2} , $0.36 \times 10^9 \text{ M}^{-1}$) was used instead of generic K_{VDBP} [27]. For heterozygous genotypes, the mean affinity of the two homozygotes was used ($K_{\text{VDBP1f/1s}}$, $0.86 \times 10^9 \text{ M}^{-1}$; $K_{\text{VDBP1f/2}}$, $0.74 \times 10^9 \text{ M}^{-1}$; $K_{\text{VDBP1s/2}}$, $0.48 \times 10^9 \text{ M}^{-1}$) [28]. In this study, bioavailable 25(OH)D referred to both genotype-constant and genotype-specific bioavailable 25(OH)D.

3. Genotyping of VDBP

DNA was extracted from all samples using a DNeasy blood & tissue kit (250; Qiagen, Hilden, Germany) following the manufacturer's instructions. Two VDBP SNPs (rs4588 and rs7041) were analyzed using real-time polymerase chain reaction with a TaqMan SNP genotyping assay kit (Thermo Fisher Scientific, Waltham, MA, USA). The functional VDBP variant was determined based on results of the 2 SNPs (rs7041 and rs4588). If there was no nucleotide change in rs7041 or rs4588, Gc1f was assigned. If T changed to G at the rs7041 SNP position, Gc1s was assigned. If C changed to A at the rs4588 SNP position, Gc2 was assigned.

4. Statistical analysis

Total serum 25(OH)D, free 25(OH)D, calculated bioavailable 25(OH)D, free 25(OH)D, and VDBP concentrations were compared between patients with endometriosis and healthy controls using the independent-sample *t*-test. The Pearson chi-square test was used to analyze correlations between the GC genotype or allele and endometriosis. Statistical analysis was performed using Excel (Microsoft Corp., Redmond, WA, USA) and IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

1. Demographic and clinical characteristics

A total of 32 women (16 with endometriosis and 16 healthy con-

Table 1. Demographic and clinical characteristics of the participants

Variable	Endometriosis patient (n = 16)	Healthy control (n = 16)	p-value
Age (yr)	34.0 (29.8–41.3)	35.5 (27.8–37.8)	0.959
Gravidity	0 (0–1.8)	2.0 (0.25–2.0)	0.601
Parity	0 (0–1.8)	1.0 (0.25–2.0)	0.765
BMI (kg/m ²)	22.7 (20.3–23.7)	21.5 (19.8–23.9)	0.967
CA-125 (IU/mL)	56.6 (24.2–194.8)	19.8 (8.4–30.5)	0.004
Serum albumin (g/dL)	4.4 (4.0–4.7)	4.4 (4.2–4.7)	0.352
ESR (0–20) (mm/hr)	16.0 (5.5–30.5)	7.0 (3.3–10.0)	0.025
CRP (0–5) (mg/L)	0.2 (0.1–0.5)	0.6 (0.4–1.2)	0.139
Enrolled season			0.643
Spring (Mar–May)	6	5	
Summer (Jun–Aug)	3	4	
Fall (Sep–Nov)	3	4	
Winter (Dec–Feb)	1	3	

Values are presented as median (interquartile range) except for the enrolled season. The statistical analysis methods used for enrolled season and other variables were the Pearson chi-square test and the independent-sample *t*-test, respectively. BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

controls) were enrolled in this study. The demographic and clinical characteristics of the endometriosis and control groups are presented in Table 1. There were no statistically significant differences in age, gravidity, parity, body mass index (BMI), serum albumin levels, C-reactive protein (CRP) levels, or enrolled season between the endometriosis and control groups. However, serum CA-125 levels and the erythro-

cyte sedimentation rate (ESR) were significantly higher in the endometriosis patients than in the control group ($p=0.004$ and $p=0.025$, respectively).

2. Comparison of total serum, bioavailable, and free 25(OH)D concentrations between the endometriosis and control groups

The total serum, bioavailable, and free 25(OH)D VDBP concentrations of patients with endometriosis and healthy controls were compared (Figure 1). The median total 25(OH)D level was 9.55 ng/mL (interquartile range [IQR], 3.00–24.41 ng/mL) in patients with endometriosis and 16.48 ng/mL (IQR, 8.36–26.00 ng/mL) in healthy controls. The median bioavailable 25(OH)D level was 1.43 ng/mL (IQR, 0.89–4.50 ng/mL) in patients with endometriosis and 1.82 ng/mL (IQR, 1.03–4.42 ng/mL) in healthy controls. The median free 25(OH)D level was 4.32 pg/mL (IQR, 2.59–10.2 pg/mL) in patients with endometriosis and 4.67 pg/mL (IQR, 2.59–10.18 pg/mL) in healthy controls. The total serum 25(OH)D level was significantly lower in the endometriosis patients than in the healthy controls ($p=0.017$). However, serum bioavailable and free 25(OH)D levels were similar between the endometriosis and control groups ($p=0.858$ and $p=0.961$, respectively).

3. Analysis of serum VDBP levels in patients with endometriosis and healthy controls

The median serum VDBP concentrations in patients with endometriosis and healthy controls were 173.06 $\mu\text{g/mL}$ (IQR, 76.39–265.08 $\mu\text{g/mL}$) and 158.58 $\mu\text{g/mL}$ (IQR, 112.68–224.08 $\mu\text{g/mL}$), respectively (Figure 2). Serum VDBP levels did not differ significantly between the endometriosis and control groups ($p=0.323$).

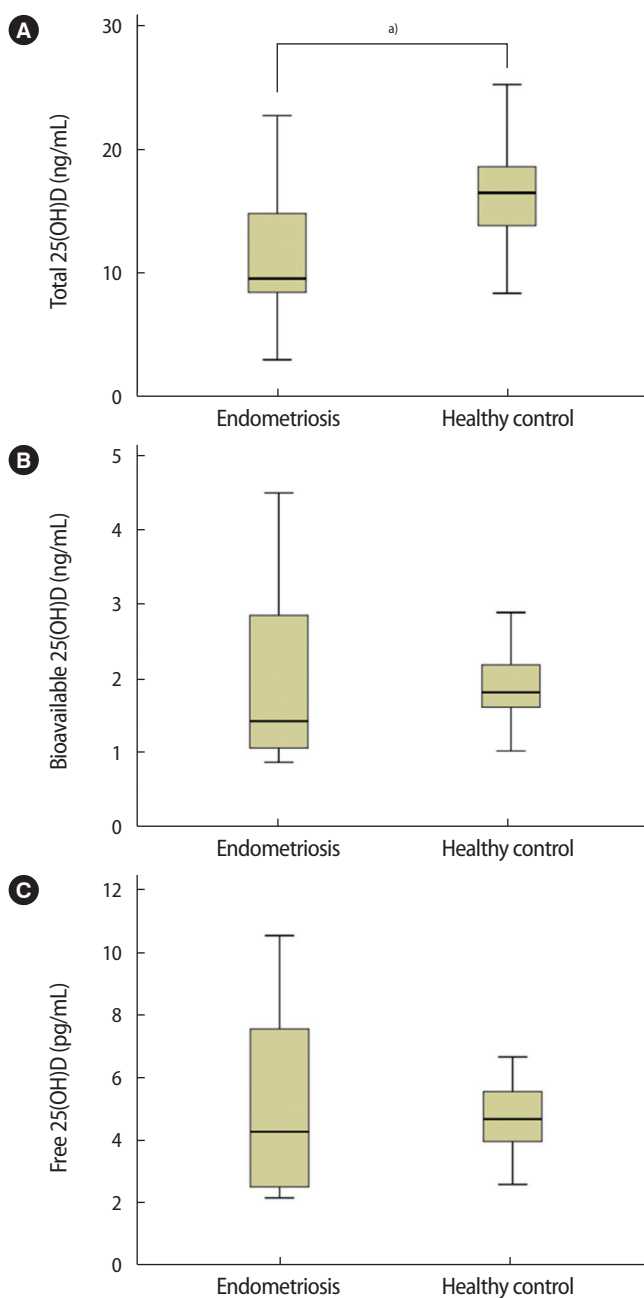


Figure 1. Comparison of serum total, bioavailable, and free 25-hydroxyl vitamin D (25(OH)D) concentrations between subjects with endometriosis and healthy controls. (A) Total 25(OH)D, $p=0.017$. (B) Bioavailable 25(OH)D, $p=0.858$. (C) Free 25(OH)D, $p=0.961$. The independent sample t -test was used for the statistical analysis. ^{a)}Indicates statistical significance.

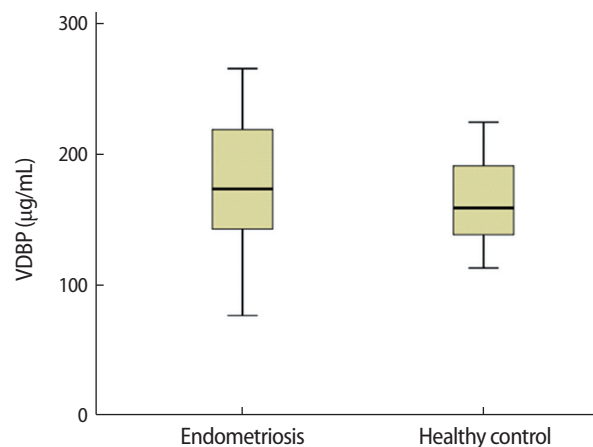


Figure 2. Comparison of serum vitamin D-binding protein (VDBP) concentrations in women with endometriosis and healthy controls ($p=0.323$). The independent-sample t -test was used for the statistical analysis.

Table 2. Genotype and allele frequencies of GC

Variable	Endometriosis patient	Healthy control	Total	p-value
Genotype frequency				0.788
<i>Gc1f/Gc1f</i>	2 (12.5)	2 (12.5)	4 (12.5)	
<i>Gc1f/Gc1s</i>	5 (31.3)	4 (25.0)	9 (28.1)	
<i>Gc1f/Gc2</i>	4 (25.0)	5 (31.3)	9 (28.1)	
<i>Gc1s/Gc1s</i>	0	1 (6.3)	1 (3.2)	
<i>Gc1s/Gc2</i>	3 (18.7)	1 (6.3)	4 (12.5)	
<i>Gc2/Gc2</i>	2 (12.5)	3 (18.7)	5 (15.6)	
Allele frequency				0.946
<i>Gc1f</i>	13 (40.6)	13 (40.6)	26 (40.6)	
<i>Gc1s</i>	8 (25.0)	7 (21.9)	15 (23.4)	
<i>Gc2</i>	11 (34.4)	12 (37.5)	23 (35.9)	

Values are presented as number (%). The Pearson chi-square test was used for the statistical analysis.

4. Analysis of genotype and allele frequencies of GC in patients with endometriosis and healthy controls

The genotype and allele frequencies of GC in patients with endometriosis and healthy controls are summarized in Table 2. The most frequent genotype in both groups was *Gc1f/Gc1s* (28.1%) and *Gc1f/Gc2* (28.1%), followed by *Gc2/Gc2* (15.6%). Among the three VDBP alleles, the most frequent allele was *Gc1f* (40.6%), followed by *Gc2* (35.9%) and *Gc1s* (23.4%). The genotype and allele frequencies were similar between the two groups ($p=0.788$ and $p=0.946$, respectively).

Discussion

In this study, we analyzed serum vitamin D (total 25(OH)D, bioavailable 25(OH)D, and free 25(OH)D) levels, as well as VDBP gene polymorphisms, in Korean women with endometriosis. Our results demonstrated that Korean women with endometriosis had lower total serum 25(OH)D concentration than controls. However, there were no significant differences in serum bioavailable or free 25(OH)D levels between patients with endometriosis and healthy controls. In addition, serum VDBP concentrations and VDBP gene polymorphisms showed no significant association with endometriosis. To the best of our knowledge, this is the first study on VDBP polymorphisms in Korean women with endometriosis.

To elucidate the relationship between serum vitamin D levels and endometriosis, we enrolled Korean women with endometriosis ($n=16$) and an equal number of healthy women as controls ($n=16$) in this study. The clinical characteristics of the subjects enrolled in this study showed that age and BMI were similar between the two groups. In our study, CA125 concentrations were higher in patients with endometriosis than in the healthy controls. A meta-analysis of CA125 for the diagnosis of endometriosis suggested that serum CA125 levels might be a useful biomarker for the noninvasive diagnosis of endometriosis [29]. Our finding is consistent with this previ-

ous meta-analysis. In addition, the endometriosis patients included in our study had endometriosis confirmed pathologically postoperatively. In other words, these patients had severe endometriosis that required surgery. Thus, the CA-125 levels in the patients with endometriosis included in our study appeared to be higher than those in the cohorts of other studies.

While the CRP elevation in the endometriosis group was not statistically significant, the higher ESR observed in the endometriosis group did reflect a statistically significant difference. The reason for this finding might be that endometriosis can change from an acute to chronic process and be accompanied by tissue destruction, as in malignancy. The inflammatory marker CRP has been shown to be upregulated in women with endometriosis, especially when examined with a high-sensitivity assay, making it possible to detect sub-clinical inflammation [30]. However, other studies were not able to identify upregulation of CRP in women with endometriosis [31,32]. In a retrospective cohort study, discrepancies between CRP and the ESR have been reported. These discrepancies might have been due to timing of various studies, with a rise in CRP manifesting before the ESR elevates, or due to the possibility that the ESR does not change in response to minor inflammation [33]. Patients with a high ESR and normal CRP levels most likely have conditions without demonstrable systemic inflammation, such as malignancy.

In our study, both endometriosis and control groups had mean serum total 25(OH)D levels of less than 20 ng/mL. A previous epidemiological study by our study group reported that over 80% of women in our local region were vitamin D-deficient [34]. The results of the present study are consistent with those of the previous study [34]. However, in the present study, we first demonstrated that although most endometriosis patients and healthy controls had vitamin D deficiency, women with endometriosis had lower total serum 25(OH)D concentrations than the control group, suggesting that low levels of vitamin D could be associated with the pathogenesis of endometriosis.

sis. A previous study of the *in vitro* effects of vitamin D on human endometriotic cells also reported that vitamin D regulates inflammation and proliferation in endometriosis, suggesting that vitamin D could be used as a therapeutic strategy to manage endometriosis [35]. Supporting this proposal, vitamin D has been reported to be involved in the development and progression of endometriosis in animal experiments. For example, Abbas et al. [36] reported the regression of endometriotic implants treated with vitamin D₃ in a rat model. Other reports have found low *in vitro* fertilization success rates when vitamin D concentrations are low in blood or follicular fluid [37]. These results are consistent with the expectation that pregnancy rates in patients with endometriosis will be low.

Although serum levels of bioavailable and free 25(OH)D were lower in the endometriosis patients, the difference between the endometriosis and control groups was not significant. The same tendency was observed for serum *VDBP* levels between the two groups. The limited sample size of our study might explain the lack of statistical significance in these results.

In our study, serum levels of *VDBP* did not differ significantly between the endometriosis and control groups. Borkowski et al. [38] found no significant difference in total *VDBP* concentrations in serum and peritoneal fluid between women with endometriosis and those without endometriosis. Using two-dimensional polyacrylamide gel electrophoresis, Ferrero et al. [39] found that one isoform of *VDBP* was present at significantly lower levels in the peritoneal fluid, but not in the plasma, of women with endometriosis than in controls. Another study of *VDBP* reported that the abundance of 25 protein spots, including acute-phase proteins and complement components, differed significantly between women with endometriosis and controls. *VDBP* protein levels were approximately three-fold higher in the endometriosis group than in the control group [24].

Polymorphisms located in genes encoding proteins mediated by vitamin D might be risk factors for endometriosis and infertility [22]. Numerous polymorphisms in *VDBP* and functional variants are known to affect vitamin D activity. Two well-known single nucleotide polymorphisms (SNPs)—rs7041 (NM_000583.3:c.1296T > G; NP_000574.2:p.Asp432Glu) and rs4588 (c.1307C > A; p.Thr436Lys)—are known to give rise to three major polymorphic isoforms of *VDBP* (Gc1F, Gc1S, and Gc2) [20]. In our study, Gc1f was the most frequent polymorphic allele in the endometriosis group (at 40.6%), consistent with a previous study on *GC* polymorphisms in various ethnic groups, which reported that the Gc1f allele was the most commonly inherited form and the most frequently reported polymorphic allele in Asian and African populations [40]. To our knowledge, research on *GC* polymorphisms is scarce and studies of *GC* polymorphisms in the Korean population are extremely rare. Faserl et al. [24] analyzed specific allele products using nanoscale liquid chromatography-electro-

spray ionization-mass spectrometry in women with endometriosis and found that the most prevalent *VDBP* Gc2 genotype in endometriosis may allow endometriotic tissues to implant in the peritoneal cavity. However, we did not find any correlation between the *VDBP* genotype and endometriosis in our study of Korean women. A study comparing 25(OH)D and *VDBP* concentrations in African-American and European-American women concluded that African-American women had lower concentrations of total 25(OH)D than did European-American women [41]. However, both groups had similar *VDBP* concentrations, suggesting that African-American women might have had lower concentrations of free 25(OH)D [41]. Although the demographic and lifestyle determinants of 25(OH)D concentrations were similar between the two groups in this study, genetic determinants may be ethnicity-specific. The relationship between *VDBP* genotype and endometriosis in our study was not statistically significant. However, the study was meaningful in that we studied the associations of *VDBP* gene polymorphisms with endometriosis in Korean women for the first time.

We acknowledge that our study has some limitations. First, the number of participants enrolled in our study was relatively small. Second, we did not have information regarding a food questionnaire to investigate dietary habits or levels of sun exposure. Third, our study did not stratify participants according to the severity of endometriosis. This needs to be overcome in further studies. Fourth, we did not use liquid chromatography-tandem mass spectrometry (LC-MS/MS), a gold standard method, to measure total 25(OH)D levels. However, the Elecsys vitamin D total kit with the Cobas e602 module (Roche Diagnostics) used in this study has been previously evaluated and reported to be a comparable assay to the LC-MS/MS method [42]. An advantage of our study was that we measured serum levels of 25(OH)D and *VDBP* in healthy women and those with endometriosis. To the best of our knowledge, this is the first study to investigate the frequency of *VDBP* gene polymorphisms in Korean women with endometriosis.

In conclusion, Korean women with endometriosis had lower total serum concentrations of 25(OH)D than controls. Serum *VDBP* concentrations and *VDBP* gene polymorphisms (rs4588 and rs7041) had no significant association with endometriosis. Further studies are needed to investigate the pathophysiology and clinical implications of 25(OH)D and *VDBP* levels in endometriosis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Min-Chul Cho	https://orcid.org/0000-0002-0609-7734
Jin Hyun Kim	https://orcid.org/0000-0003-2913-6481
Myeong Hee Jung	https://orcid.org/0000-0002-0787-2819
In Ae Cho	https://orcid.org/0000-0002-6295-4059
Hyen Chul Jo	https://orcid.org/0000-0001-9943-2863
Jeong Kyu Shin	https://orcid.org/0000-0001-9050-0874
Soon Ae Lee	https://orcid.org/0000-0002-8141-5595
Won Jun Choi	https://orcid.org/0000-0002-4887-3201
Jong Hak Lee	https://orcid.org/0000-0003-3853-0560

Author contributions

Conceptualization: MCC, WJC. Funding acquisition: MCC. Methodology: JHK, MHJ, IAC, HCJ, JKS, SAL, JHL. Writing - original draft: MCC. Writing - review & editing: WJC.

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